

### Epidemiology

C-type particles were found in ultrathin sections of kidneys, lungs and salivary glands, i.e. the organs most directly in contact with the external environment. Viral particles could also be revealed by negative staining of high-speed urinary sediments, and these sediments also caused the development of symptoms of the disease (splenomegaly, lymphadenopathy), when injected parenterally to healthy animals.

These data, combined with the natural spread of the disease to in-contact healthy baboons (among them some not bred in Sukhumi and some of another species – *P. anubis*), show that horizontal transmission of the malignant lymphoma can occur among baboons, and suggest that the virus may be present in saliva, expired air and urine.

Other data suggest that vertical transmission of virus from sick mother to fetus may also occur. Two cases of congenital malignant lymphoma were confirmed in newborn baboons, one of which died and was autopsied. Material from this baby has been successfully transmitted in two subsequent passages to other baboons. Similar results were observed in experiments on *M. arctoides*.

### Summary

The experiments described show that inoculation of two monkey species, *M. arctoides* and *P. hamadryas*, with human leukæmic blood or its filtrates causes a viral disease with the characteristics of malignant lymphoma of mixed type. The disease was passed in subsequent passages. The virus was isolated and identified as an oncornavirus of C-type by its characteristic morphological appearance and buoyant density (1.16 g/cm<sup>3</sup> in sucrose and 1.21 g/cm<sup>3</sup> in caesium chloride), and by the presence of 60-70S RNA and RNA-dependent DNA polymerase. There is some evidence that it differs immunologically from other known oncornaviruses of mammals including primates. It is postulated that both horizontal and vertical transmission of this oncornavirus can occur.

### REFERENCES

- Indzhia L V, Kokosha L V & Fomenko V N (1973) *Vestnik Akademii Meditsinskikh Nauk SSSR* 4, 40–43  
 Kokosha L V, Lapin B A, Deitchman G I & Yakovleva L A (1973) *Voprosy Virusologii* 5, 582–588  
 Lapin B A (1973) *Bibliotheca hematologica* 39, 263–268  
 Lapin B A & Yakovleva L A (1970) *Vestnik Akademii Meditsinskikh Nauk SSSR* 5, 60–71  
 Lapin B A, Yakovleva L A, Asanov N S, Kokosha L V, Tsiripova G S, Mirvis H B & Ivanov M T (1973) *Voprosy Virusologii* 1, 38–44  
 Lapin B A, Yakovleva L A, Bukaeva I A, Indzhia L V & Kokosha L V (1973) Fourth International Congress on Primatology, Symposia 4, 1–29  
 Lapin B A, Yakovleva L A, Indzhia L V, Kuksova M I, Kokosha L V, Schekolodkin V F, Lebedev V N, Bikovski A F & Lorye Y I (1973) *Vestnik Akademii Meditsinskikh Nauk SSSR* 4, 10–20

- Lapin B A, Yakovleva L A, Kuksova M I, Adzhigitov F I, Krivoshein Y S & Skurkovich S V (1967) *Byulleten' eksperimental'noi Biologii i Meditsiny* 8, 78–83  
 Yakovleva L A (1970) *Bibliotheca hematologica* 36, 761–772  
 Yakovleva L A, Lapin B A, Fomenko V N, Ivanov M T & Schekolodkin V F (1973) *Vestnik Akademii Meditsinskikh Nauk SSSR* 4, 20–31

### Professor K McCarthy and Dr F A Tosolini<sup>1</sup>

(Department of Medical Microbiology,  
The University, Liverpool, L69 3BX)

### A Review of Primate Herpes Viruses

The last twenty years have seen an ever increasing use of subhuman primates in medical and scientific research. With very few exceptions these animals are trapped in the wild and air freighted in large batches to research laboratories throughout the world. Often they will have passed through several staging posts and thus had opportunity for contact with many other species of primates, including man, as well as with animals of lower orders. Although animals which are obviously sick are not shipped for fear of incurring financial loss through immediate outbreaks of lethal disease, the pre-export scrutiny cannot detect minor infections so that on arrival in the country of destination the condition of newly arrived monkeys is often marred by a series of minor illnesses or occasionally by outbreaks of lethal disease. Many infections by viruses of the herpes group are likely to be missed because characteristically herpes infection in the natural host is trivial or completely inapparent. The full virulence of one of these viruses may not be manifest unless the virus is accidentally transmitted to a new species. The best known example of this is the infection of man by *Herpesvirus simiae* (B virus).

Twenty years ago only three primate herpes viruses were known: *Herpesvirus hominis* 1 ('herpes simplex virus'), *Herpesvirus simiae* and *Herpesvirus varicellae* ('varicella-zoster virus'). At the present time thirty-seven primate herpes virus strains are known to exist (Table 1).

Several reviews of selected primate herpes viruses have appeared in recent years (Plummer 1967, Hunt & Melendez 1969, Kalter & Heberling 1971, 1972, Hull 1968, 1973). Although *Herpesvirus simiae* is the only simian herpes virus known to infect man, there has been an understandable reluctance to pursue extensive investigations with the other simian herpes viruses. Thus, many

<sup>1</sup>Present address: Division of Microbiology, Institute of Medical and Veterinary Science, Adelaide, South Australia 5000

**Table 1**

Discovery of primate herpes viruses

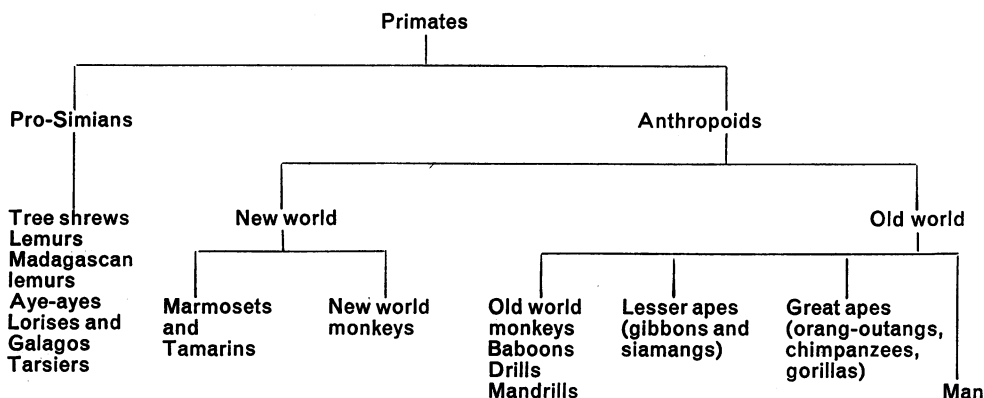
<i>Virus</i>	<i>Year</i>	<i>Reference</i>
1 <i>H. hominis</i> 1	(1919)	Löwenstein
2 <i>H. simiae</i> 'B'	(1934)	Sabin & Wright
3 <i>H. varicellae</i>	(1953)	Weller
4 Human CMV	(1956)	Smith
	(1956)	Rowe <i>et al.</i>
5 SA6	(1957)	Malherbe & Harwin
6 SA8	(1957)	Malherbe & Harwin
7 <i>H. hominis</i> 2	(1962)	Schneweis
8 SA15	(1963)	Malherbe <i>et al.</i>
9 Vervet CMV	(1963)	Black <i>et al.</i>
10 <i>H. tamarinus</i>	(1963)	Holmes <i>et al.</i>
11 EB virus	(1964)	Epstein <i>et al.</i>
12 <i>H. aotus</i>	(1966)	Sheldon & Ross
13 LVV	(1967)	Clarkson <i>et al.</i>
14 Vervet CMV	(1967)	Dreesman & Benyesh-Melnick
15 HPV	(1968)	McCarthy <i>et al.</i>
16 <i>H. saimiri</i>	(1968)	Melendez <i>et al.</i>
17 <i>H. aotus</i> (KM91)	(1968)	McCarthy & Clarkson (unpublished)
18 Rhesus CMV	(1969)	Asher <i>et al.</i>
19 <i>H. aotus</i> (KM180)	(1969)	McCarthy & Clarkson (unpublished)
20 Vervet CMV	(1969)	Smith, Thiel <i>et al.</i>
21 <i>H. aotus</i> (KM322)	(1970)	McCarthy & Clarkson (unpublished)
22 Chimpanzee herpes	(1971)	McClure & Keeling
23 Delta patas 1	(1971)	Ayres
24 <i>H. saguinus</i>	(1971)	Melendez <i>et al.</i>
25 <i>H. aotus</i> (KM338)	(1971)	McCarthy & Clarkson (unpublished)
26 <i>H. aotus</i> 1	(1971)	Daniel <i>et al.</i>
27 <i>H. ateles</i> 1	(1972)	Hull <i>et al.</i>
28 <i>H. ateles</i> 2	(1972)	Melendez, Hunt, King <i>et al.</i>
29 <i>H. ateles</i> 3	(1972)	Melendez, Castellanos <i>et al.</i>
30 <i>H. papio</i>	(1972)	Kalter & Heberling
31 Aotus CMV	(1972)	Ablashi <i>et al.</i>
32 <i>H. aotus</i> 2	(1973)	Barahona <i>et al.</i>
33 <i>H. aotus</i> 3	(1973)	Daniel <i>et al.</i>
34 Macaque herpes	(1973)	Blakely <i>et al.</i>
35 Rhesus CMV	(1973)	Frank <i>et al.</i>
36 Gorilla herpes	(1974)	Marennikova <i>et al.</i>
37 Delta patas 2	(1974)	Allen <i>et al.</i>

comparative studies between and within the different groups still have to be made, and some of the isolates listed may prove to have similar properties.

To facilitate consideration of the primate herpes viruses, a simplified classification of the primates themselves (Fig 1) has been adapted from Napier & Napier (1967). Most of the isolations of new primate herpes viruses were from man or from Old World monkeys (Table 1). As New World monkeys have come into experimental use, they have yielded an increasing proportion of new isolates. The few virus isolates that have been made from pro-simians have either not been adequately characterized or have been identified as herpes simplex virus (McCombs *et al.* 1971, McClure *et al.* 1972, Kemp *et al.* 1972) and have for those reasons been excluded from Table 1. Similarly, the isolations of herpes simplex virus from the gibbon (Smith, Yuill *et al.* 1969, Emmons & Lennette 1970), marmoset (Hunt & Melendez 1972) and owl monkey (Melendez *et al.* 1969), and the reports of a varicella-like illness in apes (Heuschele 1960, Klein & Milhaud 1971) have been excluded.

Unfortunately there are no generally accepted rules for naming new virus isolates. When the primary host has been easily ascertainable, the virus has been quite properly called after that host. However, disease may often be manifest only in a secondary host, and when the primary host is unknown many viruses have been named after the host from which they were first isolated. In some cases, the primary host may not even prove to be a primate species. A long delay may ensue before the primary host is known with certainty, so that the desirable change of name may subsequently be difficult to implement.

Since most of the viruses have only recently been isolated, relatively little is known about their

**Fig 1** *Simplified classification of primate species*

host range, laboratory properties or serological interrelationships. For the purposes of classification we have therefore made use of the nature of the disease or subclinical infection in the primary host; or more often in the secondary host in which disease first became manifest. Sometimes it has been possible to supplement this classification by information about the properties of the particular viruses. In this way we have been able to recognize four groups based primarily on disease patterns caused by herpes viruses in primates (Table 2). It is convenient to add a fifth group of viruses not known to cause any disease. Some of these viruses may need to be transferred to one of the four disease groups as new information is obtained. The possibility of one virus appearing in more than one group is not excluded.

By analogy with the disease patterns caused by nonprimate herpes viruses, it may become necessary to establish further categories. For instance, no primate analogue has yet been discovered corresponding to the adenocarcinoma of frogs described by Lucké (Granoff 1973) or to the respiratory illnesses caused by viruses such as infectious bovine rhinotracheitis or avian infectious laryngotracheitis. There is, however, some evidence associating *Herpesvirus hominis* 2 infection with cervical cancer (Rawls 1973) and *Herpesvirus hominis* 1 infection with certain epithelial tumours (Sabin & Tarro 1973).

#### *Viruses Causing Neurological or Generalized Disease*

These viruses (Table 2, columns 1 and 2) are typified by *Herpesvirus hominis* 1 and 2. *Herpes-*

*virus simiae* has been mentioned as an example of enhanced virulence on transfer to a new host species. SA8 virus occurs as a latent infection in vervet monkeys and is similar to *Herpesvirus simiae* both immunologically and in pathogenicity for rabbits. SA8 has also been isolated from healthy baboons (Kalter 1970, Malherbe 1970).

The natural host of all the above viruses is known with a reasonable degree of certainty, and this is also true of *Herpesvirus tamarinus*. This New World virus, which may be excreted by persistently infected healthy squirrel monkeys (the natural host) causes generalized lethal disease in marmosets ('tamarins') and in several other species of New World primates.

The natural hosts for the remainder of the viruses in this group are not known. *Herpesvirus ateles* 1 represents a single isolation of virus from a diseased spider monkey and is immunologically related to *Herpesvirus tamarinus*.

The virus here called *Herpesvirus aotus* was isolated by Sheldon & Ross (1966) from a fatal outbreak of disease in owl monkeys; it is immunologically related to *Herpesvirus tamarinus* (W A Holmes, personal communication). Four viruses were isolated between 1968 and 1971 (McCarthy & Clarkson, unpublished) from outbreaks of lethal disease in owl monkeys which resembled the illness reported by Sheldon & Ross. These four isolates are immunologically closely related to *Herpesvirus tamarinus*. Each differs in pathogenicity for the rabbit, ranging from minimal skin lesions following intradermal inoculation to a lethal encephalitis. One of these agents, of intermediate virulence (KM 322), has

Table 2

Patterns of infection with primate herpes viruses

Neurological or generalized disease. Cell-free virus produced in culture		Exanthematous disease. Cultured virus cell-associated (? defective)		CMV-type infection. Virus recoverable from 'healthy' animal tissues		Benign or malignant lymphoproliferative disease. No free virus in malignant tissue		No reported disease. Virus recoverable from 'healthy' animal tissues	
Old world and man (1)	New world (2)	Old world and man (3)	New world (4)	Old world and man (5)	New world (6)	Old world and man (7)	New world (8)	Old world and man (9)	New world (10)
<i>H. hominis</i> 1	<i>H. tamarinus</i>	<i>H. varicella</i>	None reported	Human CMV	Aotus CMV	EB virus	<i>H. saimiri</i>	<i>H. papio</i>	<i>H. saguinus</i>
<i>H. hominis</i> 2	<i>H. ateles</i> 1	LVV		Vervet CMV (Black <i>et al.</i> 1963)			<i>H. ateles</i> 2	SA15	<i>H. ateles</i> 3
<i>H. simiae</i> 'B'	<i>H. aotus</i> (Sheldon & Ross 1966)	HPV		Vervet CMV/SA6					<i>H. aotus</i> 1
SA8	<i>H. aotus</i> (McCarthy & Clarkson, unpublished): isolate KM91 isolate KM180 isolate KM322 isolate KM338	Delta patas 1		Vervet CMV (Dreesman & Benyesh-Melnick 1967)					<i>H. aotus</i> 3
		Chimpanzee herpes		Vervet CMV (Smith, Thiel <i>et al.</i> 1969)					
		Macaque herpes		Rhesus CMV (Asher <i>et al.</i> 1969)					
		Gorillaherpes		Rhesus CMV (Frank <i>et al.</i> 1973)					
		Delta patas 2							

provided a model system for the study of latent virus infection in the dorsal root ganglia (McCarthy 1972).

There are in fact nine virus strains derived from owl monkeys (Table 2, columns 2, 6, 10). Those in column 2 probably originated from a different host species and are clearly different from those in columns 6 and 10. The distinction between aotus CMV (column 6) and *Herpesvirus aotus* types 1, 2 and 3 (column 10) has been made on very slender grounds.

No antigenic similarity appears to exist between the Old World and the New World members of this group of viruses (Hull *et al.* 1972, McCarthy, unpublished).

#### *Viruses Causing Exanthematous Diseases*

All the viruses in this group (Table 2, columns 3 and 4) cause diseases resembling human chickenpox, though with a wide variation in virulence. The interrelationships between these viruses are not fully worked out, but they seem to fall into two subgroups. Those which were isolated from the chimpanzee and the gorilla, like varicella cause a nonlethal infection and the host range seems to be very restricted, whereas those isolated from vervet, patas or macaque monkeys can each infect a number of other species of monkey and cause a severe illness, often with a high mortality.

In tissue culture, all these agents produce changes typical of the herpes group, but no free infective virus can be detected in supernatant fluids of cell lysates. Subcultures must be made with either intact cells or particulate cell debris. The virions seen in supernatant fluids are non-infectious.

#### *Infections Caused by Cytomegaloviruses*

Postnatal human infections with cytomegalovirus are commonly silent; only rarely is disease recognizable. Simian viruses which in their laboratory properties resemble human CMV have been isolated several times (Table 2, columns 5 and 6). There have been four reports of isolations from vervet monkeys, two from rhesus and one from owl monkeys. Serological comparisons have not been made between the four vervet CMV isolates but serological cross-reactions have been reported between human vervet CMV (Dreesman & Benyesh-Melnick 1967) and between vervet and rhesus CMV (Smith, Thiel *et al.* 1969).

Although cytomegaloviruses are generally species specific when cultured *in vitro*, vervet CMV grows readily in human embryonic fibroblasts (Black *et al.* 1963).

No clinical disease has been recognized so far in monkeys.

#### *Viruses Causing Benign or Malignant Lymphoproliferative Disease*

The prototype member of this group (Table 2, columns 7 and 8) is EB virus. There now seems little doubt that this is the same agent which causes glandular fever in man. Suspicion is growing that this virus is also the cause of Burkitt's lymphoma in man and that it can also cause malignant disease in some lower primates (Epstein, Hunt & Rabin 1973, Epstein, Rabin *et al.* 1973, Shope *et al.* 1973).

*Herpesvirus saimiri* was isolated from the kidney of a healthy squirrel monkey. This species appears to be its natural host, in which no disease is caused. However, this virus has been shown to cause malignant lymphoproliferative disease in owl monkeys, cotton-topped marmosets, white-lipped marmosets, white-moustached marmosets, spider monkeys, cinnamon ringtail monkeys and vervet monkeys, as well as in rabbits, but not in common marmosets, stump-tailed macaques, rhesus, bonnet, cynomolgus or talapoin monkeys, galagos, baboons or chimpanzees (Deinhardt 1973, Hunt & Melendez 1972, Melendez, Hunt, Daniel *et al.* 1972). A similar virus was isolated from the heart tissue cultures of a squirrel monkey (Daniel *et al.* 1970).

A further oncogenic herpesvirus has been isolated by Melendez, Hunt, King *et al.* (1972) from the kidneys of a healthy black spider monkey. This causes malignant lymphoma in the cotton-topped marmoset, but has not yet been investigated as extensively as *Herpesvirus saimiri*.

#### *Viruses Not Known to Cause Disease*

Members of this miscellaneous group of herpes viruses (Table 2, columns 9 and 10) have all been isolated from healthy animals or their cultured cells. Little has been published about their behaviour or serological relationships. With the exception of SA15 all these viruses have been named after the species from which they were isolated. SA15 was initially isolated from vervet kidney tissue culture but has subsequently also been isolated from healthy baboons (Malherbe 1970). Further work may perhaps justify transfer to one of the other groups.

#### *Conclusions*

Although many new simian herpes viruses have been isolated in recent years, studies of these viruses require the utmost care and necessarily proceed slowly. The present profusion of isolations is probably the result of two factors. Firstly, the intensive study of certain species of primates and the use of their tissues for cell culture has revealed a number of latent agents; these are probably indigenous to the species from which

they have been isolated. Secondly, accidental cross-infection of primates from some other species, with the production of clinical illness, has revealed several more viruses; in many of these instances the natural host is not known. Sero-epidemiological studies are needed to define the primary hosts and the distribution of the infections in the wild.

All herpes virus infections include the possibility of virus latency, yet few studies have been made of the mechanisms of latency of the primate herpes viruses. A knowledge of these mechanisms is clearly needed for a fuller understanding of herpes virus oncogenicity. So far, only one human and two simian herpes viruses have been shown to be oncogenic, but further investigations of the other thirty-four primate herpes viruses may reveal a selective capacity for inducing malignancy when tested in an appropriate host species. The possibility that man may prove to be such a species must be kept in mind when working with these agents.

There is no accepted classification system of the primate herpes viruses and the grouping we have suggested in Table 2 may serve as an interim aid pending more detailed serological and physico-chemical studies.

**Acknowledgment:** This work was supported by a grant from the Medical Research Council.

#### REFERENCES

- Ablashi D V, Chopra H C & Armstrong G R (1972) *Laboratory Animal Science* 22, 190-195
- Allen W P, Felsenfeld A D, Wolf R H & Smetana H F (1974) *Laboratory Animal Science* 24, 222-228
- Asher D M, Gibbs C J jr & Lang D J (1969) *Bacteriological Proceedings* p 191
- Ayres J P (1971) *Laboratory Animal Science* 21, 685-695
- Barahona H H, Melendez L V, King N W, Daniel M D, Fraser C E O & Prevaille A C (1973) *Journal of Infectious Diseases* 127, 171-178
- Black P H, Hartley J W & Rowe W P (1963) *Proceedings of the Society for Experimental Biology and Medicine* 112, 601-605
- Blakely G A, Lourie B, Morton W G, Evans H H & Kaufmann A F (1973) *Journal of Infectious Diseases* 127, 617-625
- Clarkson M J, Thorpe E & McCarthy K (1967) *Archiv für die gesamte Virusforschung* 22, 219-234
- Daniel M D, Melendez L V, Hunt R D, King N W & Williamson M E (1970) *Bacteriological Proceedings* p 195
- Daniel M D, Melendez L V, King N W, Barahona H H, Fraser C E O, Garcia F G & Silva D (1973) *American Journal of Physical Anthropology* 38, 497-500
- Daniel M D, Melendez L V, King N W, Fraser C E O, Barahona H H, Hunt R D & Garcia F G (1971) *Proceedings of the Society for Experimental Biology and Medicine* 138, 835-845
- Deinhardt F (1973) In: *The Herpes Viruses*. Ed. A S Kaplan. Academic Press, London; pp 595-625
- Dreesman G R & Benyesh-Melnick M (1967) *Journal of Immunology* 99, 1106-1114
- Emmons R W & Lennette E H (1970) *Archiv für die gesamte Virusforschung* 31, 215-218
- Epstein M A, Achong B G & Barr Y M (1964) *Lancet* i, 702-703
- Epstein M A, Hunt R D & Rabin H (1973) *International Journal of Cancer* 12, 309-318
- Epstein M A, Rabin H, Ball G, Rickinson A B, Jarvis J & Melendez L V (1973) *International Journal of Cancer* 12, 319-332
- Frank A L, Bissell J A, Rowe D S, Dunnick N R, Mayner R E, Hopps H E, Parkman P D & Mayer H M jr (1973) *Journal of Infectious Diseases* 128, 618-629
- Granoff A (1973) In: *The Herpes Viruses*. Ed. A S Kaplan. Academic Press, London; pp 627-640
- Heuschele W P (1960) *Journal of the American Veterinary Medical Association* 136, 256-257
- Holmes W A, Dedmon R E & Deinhardt F (1963) *Federation Proceedings* 22, 324
- Hull R N (1968) *Virology Monographs* 2, 1-66
- (1973) In: *The Herpes Viruses*. Ed. A S Kaplan. Academic Press, London; pp 389-426
- Hull R N, Dwyer A C, Holmes A W, Nowakowski E, Deinhardt F, Lennette E H & Emmons R W (1972) *Journal of the National Cancer Institute* 49, 225-231
- Hunt R D & Melendez L V (1969) *Laboratory Animal Care* 19, 221-234
- (1972) *Journal of the National Cancer Institute* 49, 261-271
- Kalter S S (1970) In: *Infections and Immunosuppression in Subhuman Primates*. Ed. H Balner & W I B Beveridge. Munksgaard, Copenhagen; p 119
- Kalter S S & Heberling R L (1971) *Bacteriological Reviews* 35, 310-364
- (1972) *Journal of the National Cancer Institute* 49, 251-259
- Kemp G E, Losos G L, Causey O R, Emmons R W & Golding R R (1972) *African Journal of Medical Science* 3, 177-185
- Klein M & Milhaud C (1971) *Laboratory Primate Newsletter* 10, 20-23
- Löwenstein A (1919) *Münchener medizinische Wochenschrift* 66, 769-770
- McCarthy K (1972) *Journal of Clinical Pathology* 25, Suppl. (Roy. Coll. Path.), 6, 46-50
- McCarthy K, Thorpe E, Laurson A C, Heymann C S & Beale A J (1968) *Lancet* ii, 856-857
- McClure H M & Keeling M E (1971) *Laboratory Animal Science* 21, 1002-1010
- McClure H M, Keeling M E, Olberding B, Hunt R D & Melendez L V (1972) *Laboratory Animal Science* 22, 517-521
- McCombs R M, Brunschwig J P, Mirkovic R & Benyesh-Melnick M (1971) *Virology* 45, 816-820
- Malherbe H (1970) In: *Infections and Immunosuppression in Subhuman Primates*. Ed. H Balner & W I B Beveridge. Munksgaard, Copenhagen; p 120
- Malherbe H & Harwin R (1957) *British Journal of Experimental Pathology* 38, 539-541
- Malherbe H, Harwin R & Ulrich M (1963) *South African Medical Journal* 37, 407-411
- Marennikova S S, Maltseva N N, Shelukhina E M, Shenkman L S & Korneeva V I (1974) *Intervirology* 2, 280-287
- Melendez L V, Castellanos H, Barahona H H, Daniel M D, Hunt R D, Fraser C E O, Garcia F G & King N W (1972) *Journal of the National Cancer Institute* 49, 233-238
- Melendez L V, Daniel M D, Barahona H H, Fraser C E O, Hunt R D & Garcia F G (1971) *Laboratory Animal Science* 21, 1050-1054
- Melendez L V, Daniel M D, Hunt R D & Garcia F G (1968) *Laboratory Animal Care* 18, 374-381
- Melendez L V, Espana C, Hunt R D, Daniel M D & Garcia F G (1969) *Laboratory Animal Care* 19, 38-45
- Melendez L V, Hunt R D, Daniel M D, Fraser C E O, Barahona H H, Garcia F G & King N W (1972) In: *Oncogenesis and Herpes Viruses*. Ed. P M Biggs *et al.* International Agency for Research on Cancer, Lyon, France; pp 451-461
- Melendez L V, Hunt R D, King N W, Barahona H H, Daniel M D, Fraser C E O & Garcia F G (1972) *Nature New Biology* 235, 182-184
- Napier J R & Napier P H (1967) *A Handbook of Living Primates*. Academic Press, London
- Plummer G (1967) *Progress in Medical Virology* 9, 302-340
- Rawls W E (1973) In: *The Herpes Viruses*. Ed. A S Kaplan. Academic Press, London; pp 291-325
- Rowe W P, Hartley J W, Waterman S, Turner H C & Huebner R J (1956) *Proceedings of the Society for Experimental Biology and Medicine* 92, 418-424
- Sabin A B & Tarro G (1973) *Proceedings of the National Academy of Sciences of the USA* 70, 3225-3229
- Sabin A B & Wright A M (1934) *Journal of Experimental Medicine* 59, 115-136
- Schneweis K-E (1962) *Zeitschrift für Immunitätsforschung und experimentelle Therapie* 124, 24-48
- Sheldon W G & Ross M A (1966) Report No. 670, US Army Medical Research Laboratory, Fort Knox, Kentucky; pp 1-21
- Shope T, Dechairo D & Miller G (1973) *Proceedings of the National Academy of Sciences of the USA* 70, 2487-2491

Smith K O, Thiel J F, Newman J T, Harvey E, Trousdale M D, Gehle W D & Clark G (1969) *Journal of the National Cancer Institute* 42, 489-496  
 Smith M G (1956) *Proceedings of the Society for Experimental Biology and Medicine* 92, 424-430  
 Smith P C, Yuill T M, Buchanan R D, Stanton J S & Chaicumpa V (1969) *Journal of Infectious Diseases* 120, 292-297  
 Weller T H (1953) *Proceedings of the Society for Experimental Biology and Medicine* 83, 340-346

**Dr F A Tosolini<sup>1</sup>**  
**and Professor K McCarthy**  
*(Department of Medical Microbiology,  
 The University, Liverpool, L69 3BX)*

### **Herpes Virus Latency in the Nervous System [Abridged]**

Each of the experimental systems available for the study of herpes virus latency leaves something to be desired. A new herpes virus isolated from a naturally-infected owl monkey *Aotus trivirgatus* (McCarthy & Clarkson, unpublished) had the advantage of giving rise to cutaneous lesions associated with a dorsal root ganglionitis. The infection, reminiscent of pseudorabies in cattle, was always lethal in the owl monkey. However, rabbits inoculated intradermally with the virus developed a limited disease, manifest as a local skin lesion associated with dorsal root ganglionitis, and virus persisted as a latent infection in the dorsal root ganglion (DRG).

Adult rabbits inoculated with the virus intradermally on the flank developed an erythematous papule at the inoculation site at 2 days. The lesion reached a maximum diameter of 10-12 mm by 4 days, started to regress at 7 days, and was healed by 2 weeks after infection. Generalized infection did not occur. At 5-6 days after infection, severe local irritation occurred and unless restrained by a collar, the rabbit would bite and scratch continuously at the skin in the region of the inoculation site, causing severe excoriation. Between 6 and 8 days after infection, loss of sensation developed in the skin around the lesion, as shown by lack of response to pinprick. The sensory loss extended to involve the whole of the dermatome in which the lesion was situated, and remained for 4-6 weeks before starting a slow recovery, which was sometimes incomplete. The radicular sensory disturbances were suggestive of a ganglionitis, which was confirmed histologically, and the involvement of a single dermatome suggested that the virus had spread from the skin, up the sensory nerve to the corresponding spinal ganglion.

<sup>1</sup>Present address: Division of Microbiology, Institute of Medical and Veterinary Science, Adelaide, South Australia 5000

From 6 to 12 days after infection of the rabbit, virus could be isolated from homogenized extracts of the skin lesion and corresponding DRG, cytopathic effects (CPE) appearing in 24-48 hours in cell monolayers. Homogenates of skin or DRG taken from rabbits later than 12 days after infection never yielded virus on culture. No virus was detected in blood, brain, liver, spleen or kidney.

To determine whether virus remained in a latent form in the DRG of recovered rabbits, attempts were made to 'rescue' the virus, by explanting the ganglion as organ cultures. Each ganglion was chopped into 10-20 fragments and the pieces, which contained intact ganglion cells, were placed on VERO cell monolayers. By this method, virus has been isolated from the DRG of every one of 60 rabbits examined, even animals infected as long as 18 months previously. Whereas free virus in acutely infected ganglia produced a CPE in VERO cells in 24-48 hours, in ganglia from these recovered rabbits no virus was detectable until at least 8 days after explantation of ganglion fragments. Indeed, periods of up to 104 days have elapsed before this *in vitro* reactivation of virus has occurred. Using similar explant techniques, we have never recovered virus from skin after the acute stage of infection, nor from other organs.

Attempts are being made to provoke reactivation of the infection *in vivo*. Development of a reliable method of reactivation of virus in the DRG will greatly facilitate investigation of the state of the viral genome during latency, and the types of cell in which the virus persists.

*Acknowledgment:* This work was supported by a grant from the Medical Research Council.

**Professor M A Epstein** (*Department of Pathology, University of Bristol*) gave a general review of the topic.

### REFERENCES

- Epstein M A (1971) *Lancet* i, 1344-1347
- Epstein M A & Achong B G (1973a) *Annual Review of Microbiology* 27, 413-436
- (1973b) *Lancet* ii, 836-839
- Epstein M A, Hunt R D & Rabin H (1973) *International Journal of Cancer* 12, 309-318
- Epstein M A, Rabin H, Ball G, Rickinson B A, Jarvis J & Melendez L V (1973) *International Journal of Cancer* 12, 319-332
- Epstein M A, zur Hausen H & Ball G (1975) *International Journal of Cancer* (in press)

*Meeting 19 June 1974*

There was a visit to the laboratories of the Huntingdon Research Centre, Huntingdon.